UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,207	10/27/2003	Ekambar R. Kandimalla	HYB-005US7	3842

7590 03/31/2008

WAYNE A. KEOWN
SUITE 1200
500 WEST CUMMINGS PARK
WOBURN, MA 01801

EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
03/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/694,207	KANDIMALLA ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-38 and 55-70* is/are pending in the application.

4a) Of the above claim(s) *27, 30-33, 36-38, 56, 59-65 and 68-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26, 28-29, 34-35, 55, 57-58 and 66-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-25 and 39-54 are cancelled.

Claims 26, 30, 34, 36 and 38 have been amended.

Claims 55-70 have been added.

2. Claims 27, 30-33, 36-38 and newly added claims 56, 59-65 and 68-70 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 26, 28-29, 34-35, 55, 57-58 and 66-67 are under consideration.

4. This Office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

5. The objection to the cross reference to related applications at pg. 1 of the specification as requiring updating is withdrawn in view of the amendments to the specification filed 12/20/2007.

6. The objection to the description of the figures filed 10/25/2006 because parts of Figures 1-26 (i.e., parts A, B, C) are not described is withdrawn in view of the amendments to the specification filed 12/20/2007.

7. The objection to the title as not descriptive is withdrawn in view of applicants' remarks filed 12/20/2007.

8. *All rejections set forth in the previous Office Action mailed 8/6/2007 are withdrawn in view of the amendments to the claims.*

New Grounds of Objections/Rejections

9. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Newly presented claim 55 recites an immunostimulatory

oligonucleotide compound comprising an immunostimulatory dinucleotide of formula C*pG*, wherein C* is a non-natural pyrimidine nucleoside, and G* is a non-natural purine nucleoside. The specification does not disclose nor define an immunostimulatory dinucleotide of formula C*pG*. Thus, the specification does not provide proper antecedent basis for the newly added formula "C*pG*" as presently claimed.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 26, 28-29, 34-35, 55, 57-58 and 66-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2163).

In the instant case, the claims are directed to methods of generating an immune response or treating cancer in a patient comprising administering an immunostimulatory

oligonucleotide compound comprising an immunostimulatory dinucleotide of formula C*pG, wherein C* is a non-natural pyrimidine nucleoside selected from the group consisting of 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil, and G is a natural purine nucleoside and wherein the immunostimulatory dinucleotide is conjugated to an antigen or vaccine wherein conjugation is to the 3'-end of the oligonucleotide compound and wherein the immunostimulatory oligonucleotide is administered with a chemotherapeutic agent. Further, the claims are drawn to methods of generating an immune response or treating cancer in a patient comprising administering an immunostimulatory oligonucleotide compound comprising an immunostimulatory dinucleotide of formula C*pG*, wherein C* is a non-natural pyrimidine nucleoside, and G* is a non-natural purine nucleoside and wherein the immunostimulatory dinucleotide is conjugated to an antigen or vaccine wherein conjugation is to the 3'-end of the oligonucleotide compound and wherein the immunostimulatory oligonucleotide is administered with a chemotherapeutic agent.

The specification teaches (pg. 11) that the term "immunostimulatory oligonucleotide compound" means a compound comprising an immunostimulatory dinucleotide, without which the compound would not have an immunostimulatory effect. The specification discloses that CpG is one such immunostimulatory dinucleotide and sets forth CpG immunostimulatory dinucleotide analogs comprising a cytosine analog or a guanosine analog (pg. 12). Further, with respect to the cytosine analogs, the specification discloses a single CpG oligonucleotide comprising cytosine analogs, particularly 5-hydroxycytosine or N4-ethylcytosine, which stimulate lymphocyte proliferation (e.g., see Example 2) and can be modulated significantly by incorporating appropriate chemical modifications in the 5'-flanking sequence, suggesting that these cytosine analogs in a CpG-motif are recognized as part of an immunostimulatory motif (e.g., see pg. 29). The specification also discloses that when the cytosine of the CpG-motif is replaced with uracil, no immunostimulatory activity was observed (see pg. 29). The specification does not disclose a single immunostimulatory oligonucleotide comprising an immunostimulatory dinucleotide C*pG*, where C* is a non-natural pyrimidine nucleoside and G* is a non-natural purine nucleoside. The specification

does not disclose the administration of an immunostimulatory oligonucleotide comprising the formula C*pG, wherein C* is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil, or the administration of an immunostimulatory oligonucleotide comprising the formula C*pG*, wherein C* is a non-natural pyrimidine nucleoside and G* is a non-natural purine nucleoside for generating an immune response in a patient or for treating cancer in a patient.

The written description of the present application only sets forth a single immunostimulatory oligonucleotide comprising the formula C*pG, wherein C* is 5-hydroxycytosine or N4-ethylcytosine that stimulates lymphocyte proliferation, however, the claims encompass thousands of immunostimulatory oligonucleotides that differ in length and sequence, and which generate an immune response in a patient or treat cancer in a patient. Further, the written description of the present application does not set forth a single species of immunostimulatory oligonucleotide comprising the formula C*pG* wherein C* is a non-natural pyrimidine nucleoside and G* is a non-natural purine nucleoside and which generates an immune response in a patient or treats cancer in a patient. The structures of the immunostimulatory oligonucleotides comprising the formula C*pG, wherein C* is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil that generate an immune response in a patient or treat caner in a patient are not known and the genus is inclusive to a variety of subgenera having disparate structures and functions. Similarly, the immunostimulatory oligonucleotide comprising the formula C*pG* wherein C* is a non-natural pyrimidine nucleoside and G* is a non-natural purine nucleoside that generate an immune response in a patient or treat caner in a patient are not known and the genus is inclusive to a variety of subgenera having disparate structures and functions. Thus, the instant disclosure does not provide sufficient written description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus of

immunostimulatory oligonucleotides comprising the formula C*pG*, or the various subgenera of immunostimulatory oligonucleotides comprising the formula C*pG, wherein C* is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil that generate an immune response in a patient or treat caner in a patient. See *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406.

Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]. " See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." For example, as discussed supra, the specification discloses that a CpG oligonucleotide comprising the cytosine analogs, particularly 5-hydroxycytosine or N4-ethylcytosine, can be modulated significantly by incorporating appropriate chemical modifications in the 5'-flanking sequence, suggesting that these cytosine analogs in a CpG-motif are recognized as part of an immunostimulatory motif. The specification also discloses that when the cytosine of the CpG-motif is replaced with uracil, no immunostimulatory activity was observed. Similarly, the relevant CpG immunostimulatory oligonucleotide art teaches that the length, sequence and backbone modification can alter the immunostimulatory properties of CpG oligonucleotides. Vollmer et al (Antisense and Nucleic Acid Drug Development, 12:165-175, 2002) teach that both thymidine content and length of thymidine stretches affect CpG-mediated immunostimulation and oligonucleotides with methylated CpG motifs have length-dependent immunostimulatory effects (e.g., see pg. 173 and Figs. 2-

4). Vollmer et al also discloses that poly-G sequences have independent immune effects and can modulate the activity of CpG motifs in either an agonistic or antagonistic fashion (see pg. 166 2nd col.). Verthelyi et al (The Journal of Immunology, 168:1659-1663, 2002, cited on PTO-892 mailed 8/6/07) states that "[D]ue to evolutionary divergence in CpG recognition between species, ODN that are highly active in rodents are poorly immunostimulatory in primates, and vice versa" (e.g., pg. 1659, left col.) and "CpG ODN that activate human immune cells in vitro are only weakly immunostimulatory in mice" (e.g., pg. 1662, Discussion, first par.). Dittmer et al (Current Opinion in Microbiology, 6:472-477, 2003, cited on PTO-892 mailed 8/6/07) reports that "[U]nfortunately, CpG-ODN that optimally stimulate mouse cells were only weakly effective in human cells, thus they could not be used for the treatment of humans" (e.g., pg. 472, right col., bottom par.). Thus, one of skill in the art could not predict the operability of any other species of immunostimulatory oligonucleotides comprising an immunostimulatory dinucleotide having the formula C*pG or C*pG* other than those disclosed. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. *In re Smith* 173 USPQ 679, 683 (CCPA 1972).

Further, it is not sufficient to define a substance solely by its principal biological property, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function". Similarly, the function of generating an immune response or being "immunostimulatory" does not distinguish any immunostimulatory oligonucleotide having the formula C*pG or C*pG* from others having the same activity or function and as such, fails to satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or

function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of genus of immunostimulatory oligonucleotides comprising the formula C*pG*, or the various subgenera of immunostimulatory oligonucleotides comprising the formula C*pG, wherein C* is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil that generate an immune response in a patient or treat caner in a patient, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddles v.Baird*, 30 USPQ2d 1481, 1483. In *Fiddles v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

20. No claim is allowed.

21. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643